REMARKS

Claims 148, 159, 169, 180, 190, and 201 have been canceled. No new matter has been added by way of amendment. Claims 147, 150-153, 155-156, 158, 160-163, 165-166, 168, 171-174, 176, 177, 179, 181-184, 186-187, 189, 192-195, 197-198, 200, 202-205, and 207-208 will be pending upon entry of the instant amendment.

Applicants acknowledge and appreciate the telephone interview conducted with Examiner Turner on September 8, 2005. Applicants appreciated the opportunity to discuss the non-art based and art-based issues with Examiner Turner.

Election/Restrictions

Applicants appreciate withdrawal of the species election with respect to a single species of chemokine.

Double Patenting

Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, and 207-208 were rejected by the Examiner under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 6,528,625. Specifically, the Examiner argued that the "instant claims are rendered obvious in view of the '625 patented claims directed to HB-12366 (2D7) antibody, antigen binding fragment, antibody producing hybridoma, compositions and test kit with properties including all limitations as instantly recited. Applicants note in the Office action mailed June 23, 2005, the Examiner stated that "Applicants assert that a terminal disclaimer has been filed" and "no terminal disclaimer was found within the submission of 4-4-05 or previous."

Applicants respectfully point out that a terminal disclaimer has not yet been filed, rather the statement on page 12 of the response filed April 1, 2005 indicated "Applicants will file a Terminal Disclaimer to overcome the Examiner's obviousness-type double patenting rejection as appropriate upon notice of otherwise allowable subject matter in the present application." Applicants reiterate this position, as this will permit Applicants to assess the appropriateness of the rejection in view of the claims as ultimately indicated to be allowable, since it is possible that the claims may change during the course of prosecution.

Priority

Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, and 207-208 were rejected by the Examiner under 35 USC §120 as not complying with one or more conditions for receiving the benefit of an earlier filing date. The Examiner stated that claims 147-210 are directed to a subgenus of antibodies not supported by the specification or within the noted priority documents as originally filed. Specifically, the Examiner argued that the claims "are directed to a subgenus of CCR5 antibodies which binds '*human* CCR5' wherein the antibody or fragment is further capable of inhibiting binding of *chemokines* (MIP-1α, MIP-1β and RANTES) *or combination thereof*, to human CCR5 and which *inhibits one or more functions associated with binding of a chemokine to the receptor.*"

The Examiner further stated,

> "these limitations differ from the disclosure as directed at p. 11-12, to antibodies or antigen binding fragments that inhibit binding of a '*ligand*' and '*one or more functions mediated by CCR5 in response to the ligand*'. Moreover, specific support for the further subgenus of these antibodies that are chimeric, human, humanized, binds the second extracellular loop and inhibits HIV infection are not specifically noted."

Applicants respectfully disagree. As the Examiner pointed out, the disclosure for example at pages 11-12, is directed to antibodies or antigen binding fragments that inhibit binding of a "ligand" and "one or more functions mediated by CCR5 in response to the ligand". In addition, Applicants point out that the specification, for example at page 28, lines 15-20, teaches that,

> "a "**ligand**" of a mammalian CCR5 protein refers to a particular class of substances which bind to a mammalian CCR5 protein, including natural ligands and synthetic and/or recombinant forms of natural ligands, as well as infectious agents having a tropism for mammalian CCR5 positive cells (e.g., viruses such as **HIV**). A natural ligand of a selected mammalian receptor is of a mammalian origin which is the same as that of the mammalian CCR5 protein (e.g., a chemokine such as **RANTES, MIP-1α, MIP-1β**)." (emphasis added)

In several places in the specification as filed, including for example at page 3, line 27, and at page 15, lines 26-27, the term "ligand" is further defined as " RANTES, MIP-1α, MIP-1β, human immunodeficiency virus (HIV)".

Thus, Applicants submit that the claims are indeed directed to a genus of antibodies contemplated and supported by the application as filed.

Furthermore, Applicants point to support in the priority applications as delineated in the table sent by facsimile to the Examiner in preparation for the telephone interview on September 8, 2005, and as filed on April 1, 2005, in a previous response to Office action (attached for Examiner's convenience as Appendix A). This table outlines specific support in the instant specification and that of the parent application U.S. Patent Application Serial No. 08/893,911 (filed July 11, 1997) for all the claim limitations, including:

- Human CCR5
- Chemokines (MIP-1α, MIP-1β, and RANTES) or combination thereof
- Inhibits one or more functions associated with binding of a chemokine to the receptor
- Human antibodies
- Chimeric antibodies
- Humanized antibodies
- Binds the second extracellular loop
- Inhibits HIV infection

Therefore, Applicants believe the priority date assigned to all the limitations mentioned above should be at least that of the filing date of the parent application, U.S. Patent Application Serial No. 08/893,911 (July 11, 1997).

Applicants further point out that specific support can be found in the grandparent application, U.S. Patent Application Serial No. 08/739,507 (filed October 28, 1996) as described in the table for the following limitations:

- Human CCR5
- Chemokines (MIP-1α, MIP-1β, and RANTES) or combination thereof
- Inhibits one or more functions associated with binding of a chemokine to the receptor
- Chimeric antibodies
- Humanized antibodies
- Inhibits HIV infection

Therefore, Applicants believe the priority date assigned to the limitations mentioned above should be that of the filing date of the grandparent application, U.S. Patent Application Serial No. 08/739,507 (October 28, 1996).

Applicants respectfully request reconsideration and withdrawal of the objection regarding priority, and request assignment of earliest effective filing date of October 28, 1996 for all limitations except "human" antibodies, and "binds the second extracellular loop" which should be given the earliest effective filing date of July 11, 1997.

Claim Objections

Claims 148, 159, 169, 180, 190, 201, and 204 were objected to under 37 CFR §1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner argued that the claims "do not further limit the parent or independent claims because the parent or independent claims already specify that the antibody or antigen binding fragment binds/has specificity for human chemokine receptor 5."

Applicants respectfully traverse this rejection. In an effort to expedite prosecution, Applicants have canceled claims 148, 159, 169, 180, 190, and 201, rendering this rejection moot.

Applicants respectfully point out that claim 204, reciting a test kit of claim 200 wherein the antibody or antigen binding fragment is a human antibody or antigen binding fragment, does indeed further limit the subject matter of claim 200 (a test kit comprising *an antibody or antigen binding fragment* which binds a human CCR5) as the previous claim is not limited to human antibodies, rather to antibodies that bind human CCR5. Thus, Applicants respectfully request reconsideration and withdrawal of the objection of claim 204 under 37 CFR §1.75(c).

The Rejection of Claims 166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, and 207-208 Under 35 USC §101 Should Be Withdrawn

Claims 166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, and 207-208 were rejected by the Examiner under 35 USC §101 as being directed to non-statutory subject matter. Specifically, the Examiner argued that the claims "do not reflect isolation, or the hand of man," and that the term "isolated" should be inserted to recite "an isolated antibody or antigen binding fragment thereof..."

Applicants respectfully traverse the rejection. Applicants respectfully point out that claim 158, from which claim 166 depends, has previously been amended to recite "an isolated antibody or antigen binding fragment thereof..." in Applicants' response filed April 1, 2005 (see pages 3 and 15).

In addition, Applicants submit that claims 168 and 179, and claims 189 and 200, and claims dependent therefrom, are directed to compositions comprising an antibody or antigen binding fragment thereof and a physiologically acceptable vehicle or carrier, and to test kits comprising an antibody or antigen binding fragment thereof and one or more ancillary reagents, respectively. Applicants submit that the antibodies or antigen binding fragments in such compositions and kits are not products of nature, and thus the claims are necessarily directed to statutory subject matter. Thus, Applicants respectfully request

reconsideration and withdrawal of the rejection of claims 166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, and 207-208 under 35 USC §101.

The Rejection of Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, and 207-208 Under 35 USC §112, First Paragraph (Enablement) Should Be Withdrawn

Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, and 207-208 were rejected under 35 USC §112, first paragraph, "because the specification, while being enabling for antibodies or antigen binding fragments thereof that inhibit binding of chemokine ligands MIP-1α, MIP-1β, and RANTES to human CCR5, and for the specific deposits of antibodies 5C7 and 2D7...does not reasonably provide enablement for antibodies with such functional recitations specific to chemokine binding, functions associated with binding of a chemokine to the receptor to antibodies or to specific epitope regions such as the second extracellular loop."

In particular, the Examiner stated that

> "the aforementioned claims remain drawn generically to any chemokine capable of binding human CCR5. As previously set forth, only chemokines MIP-1α, MIP-1β, and RANTES are disclosed as binding human CCR5."

Applicants respectfully point out that every independent claim (claims 147, 158, 168, 179, 189, and 200) recites the defined list of chemokines, MIP-1α, MIP-1β, and RANTES. Thus, the claims are not generically drawn to "any chemokine" but rather to the list defined in each base claim, and therefore, the instant claims are enabled with respect to chemokine binding.

Further, regarding the claimed characteristics of the claimed antibodies (inhibition of chemokine binding, wherein the chemokine is MIP-1α, MIP-1β, and RANTES as well as inhibition of one or more functions associated with binding of the chemokine to the receptor, and inhibition of HIV infection), the Examiner argued that "the claims fail to recite the epitope specificity apparently required for conveying these properties, i.e., specificity for the second extracellular loop." Applicants respectfully point out that every independent claim (claims 147, 158, 168, 179, 189, and 200) recites the limitation "which binds to the second extracellular loop of a human chemokine receptor 5 (CCR5)..." Thus, the instant claims do not "fail to recite the epitope specificity" but rather include the specificity required, (*i.e.* binds to the second extracellular loop of CCR5), and therefore, the instant claims are enabled with respect to epitope specificity required for conveying the claimed characteristics.

Applicants respectfully submit, in view of the foregoing remarks, that the rejection of claims under 35 USC §112 first paragraph (enablement) is improper, as the specification **is** enabling for a person of ordinary skill in the art to make and use the claimed invention commensurate with the scope of the claims as amended. Applicants respectfully request reconsideration and withdrawal of this rejection.

The Rejection of Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, and 207-208 Under 35 USC §112, First Paragraph (Written Description) Should Be Withdrawn

Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, and 207-208 were rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. The Examiner took the position that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner argued that

> "absent a sufficient description of the receptor-ligand pairs, or a means for immediately recognizing those chemokines that readily bind, there is not adequate written description support of the genus as directed to antibodies or antigen binding fragments that inhibit binding of any chemokine to the human CCR5 receptor..."

Applicants respectfully disagree and point out that indeed the genus of chemokines which bind CCR5 is defined such that each independent claim recites "wherein the chemokine is MIP-1α, MIP-1β, RANTES or a combination thereof," thus obviating the rejection with respect to inhibition of binding of chemokines to the receptor.

The Examiner continued,

> "the specification teaches the apparent requirement for the antibody or antigen binding fragment to be specific to the second extracellular loop in order for the antibodies to provide the noted functional characteristics, yet such is not an element of the claims, nor is there sufficient support to denote that this division is a further sub-species or sub-genus readily contemplated by Applicnats (sic)."

Applicants disagree and respectfully point out that indeed every independent claim (claims 147, 158, 168, 179, 189, and 200) recites the limitation "which binds to the second extracellular loop of a human chemokine receptor 5 (CCR5)..." Thus, contrary to the Examiner's assertion, the instant claims do indeed recite the requirement of binding to the second extracellular loop of CCR5.

Next, regarding recitations directed to inhibiting HIV infection (claims 158, 179, and 200, and claims dependent therefrom) the Examiner states,

> "the specification teaches that monoclonal antibodies to the amino terminus or second extracellular loop were capable of inhibiting HIV binding and entry...In contrast, only antibodies to the second extracellular loop of CCR5 were capable of inhibiting binding of chemokines MIP-1α, MIP-1β and RANTES to human CCR5 and inhibiting HIV binding and entry. These specifics are not limitations of the claims."

Applicants disagree and respectfully point out that these specifics (binding to the second extracellular loop, inhibiting binding of chemokines MIP-1α, MIP-1β and RANTES, and inhibiting HIV infection) are indeed limitations of every independent claim directed to inhibition of HIV infection (claims 158, 179, and 200).

Furthermore, as the Examiner has pointed out,

> "Applicants maintain that selection for example based on HIV inhibition would not necessarily lead to antibodies specific to the 2nd extracellular loop and which inhibit binding of the noted chemokines MIP-1α, MIP-1β and Rantes. Applicants specification establishes the principle that the chemokine binding site of MIP-1α, MIP-1β and Rantes is within the 2nd extracellular loop of human CCR5 and that this portion is also responsible for the additionally recited property of inhibiting HIV entry."

The Examiner argued that the prior art (without mentioning which prior art reference(s) to which she is referring) "teaches selection of antibodies based on the aforementioned criteria...and specifically guides to the 2nd extracellular loop for these properties."

Applicants respectfully disagree. For example, Olson et al. teaches that HIV entry mediated by CCR5 does not necessarily require binding to the second extracellular loop of CCR5, and Hoxie teaches that their screen for antibodies capable of blocking HIV infection would not necessarily lead to antibodies which bind CCR5 at all. In fact, of the eight antibodies described by Hoxie, only one even bound a cellular protein (CXCR4) — and none of the antibodies described by Hoxie bind CCR5. Applicants maintain that selection *based on HIV inhibition* would **not necessarily** lead to antibodies specific to the second extracellular loop of CCR5 and which inhibit binding of the noted chemokines MIP-1α, MIP-1β and RANTES. Thus, contrary to the Examiner's assertion, the art does not "specifically guide" to the second extracellular loop for the claimed characteristics of the claimed antibodies.

Therefore, the specification is sufficiently descriptive so as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, according to 35 USC §112, first paragraph. Applicants respectfully request reconsideration and withdrawal of the rejection of claims under 35 USC §112, first paragraph (written description).

The Rejections of Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, and 207-208 Under 35 USC §102 Should Be Withdrawn

For anticipation under 35 USC §102, the reference must teach every aspect of the claimed invention either explicitly or impliedly. Any feature not directly taught must be inherently present (MPEP §706.02(IV)). For a reference to anticipate by inherency, it is required that "the prior art necessarily functions in accordance with, or includes, the claimed limitations." Atlas Powder Co. v. IRECO Inc., 190 F.3d 1342, 1347 (Fed Cir. 1999). Furthermore, inherency "may not be established by probablilites or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." Continental Can Co. USA v. Monsanto Co. 948 F.2d 1264, 1269 (Fed Cir. 1991).

Applicants traverse the rejection and respectfully submit that none of the references cited as anticipatory (i.e. Li et al., Hoxie, and Littman et al.) teaches each and every aspect of the claimed invention either explicitly or impliedly. In addition, the supporting references for each of Li, Hoxie, and Littman do not evidence that the missing aspects of each are inherently present.

The antibodies of the instant invention have the following limitations in all independent claims:

1) binds to the second extracellular loop,
2) of a human chemokine receptor 5 (CCR5),
3) inhibits binding of a chemokine to the receptor,
4) wherein said chemokine is MIP-1α, MIP-1β, RANTES, or a combination thereof,
5) inhibits one or more functions associated with binding of the chemokine to the receptor,

and, in independent claims drawn to antibodies which inhibit HIV infection (claims 158, 179, and 200) the following limitation always appears in combination with 1) above (binds to the second extracellular loop):

6) wherein said antibody or antigen binding fragment thereof additionally inhibits HIV infection.

such that the antibodies of claims 158, 179, and 200, and claims dependent therefrom, both bind the second extracellular loop **and** inhibit HIV infection. Applicants submit that the references cited do not teach every aspect of the claimed invention either explicitly or impliedly, and are therefore not proper anticipatory references under 35 USC §102, as described below.

Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, and 207-208 were rejected under 35 USC §102 (e) by the Examiner as being anticipated by Li et al. (U.S. Patent No. 6,025,154) as evidenced by Wu et al. (J Exp Med, October 1997; 186(8) 1373-1381), Samson et al. (JBC, October 1997; 272(40):24934-41), Raport et al. (JBC, July 1996; 271:17161-17166), Combadiere et al. (J Leukoc Biol, July 1996; 60:147-152), and Atchison (Science, December 1996; 274:1924-1926).

Applicants respectfully disagree. Contrary to the Examiner's assertion, Li et al. does not teach each and every aspect of the invention. Li et al. is silent with respect to identity of ligands/chemokines which bind CCR5, and provides no working examples of antibodies which bind CCR5 in any manner. In addition, the screen of Li et al. does not necessarily result in identification of antibodies specific to the second extracellular loop of CCR5. Furthermore, Wu et al., which was published after the filing of the instant application, teaches that no antibodies studied prior to Wu et al. were able to block ligand binding, further demonstrating that the characteristics of instant claimed antibodies are not necessarily inherent in antibodies identified by the means of Li's screen.

Samson et al. describes that the "NH_2 terminus and the **first extracellular loop** of CCR5 are responsible for the specificity of the interaction with M-tropic HIV-1 strains" (page 23934, second column, first full paragraph; emphasis added). In fact, they emphasize that "it is clear that the regions of CCR5 involved in chemokine ligand specificity, and in the specificity of cofactor usage for various HIV-1 strains **are not identical**" (page 24940, column 1-2, bridging sentence; emphasis added). Thus, Samson et al. fails to demonstrate that the elements missing in Li et al. are **necessarily inherent** in Li et al.

Raport et al. describes the identification and characterization of a cDNA encoding CCR5 and disclose that the encoded receptor binds RANTES, MIP-1α, and MIP-1β. However, Raport et al. does not teach any antibody to CCR5 and are silent with respect to relevance of the second extracellular loop of CCR5 to generation of antibodies with the claimed characteristics of the instant invention. Thus, Raport et al. fails to demonstrate that the elements missing in Li et al. are **necessarily inherent** in Li et al.

Combadiere et al. teaches the cloning of a CCR5 variant whose amino acid sequence differs from the amino acid sequence of CCR5 disclosed in Samson et al. at amino acid 90. However, like Raport et al., Combadiere et al. does not teach any antibody to CCR5 and are silent with respect to relevance of the second extracellular loop of CCR5 to generation of antibodies with the claimed characteristics of the instant invention. In addition, Combadiere et al. makes no mention of which regions of CCR5 may be involved in HIV binding. Thus, Combadiere et al. fails to demonstrate that the elements missing in Li et al. are **necessarily inherent** in Li et al.

Atchison et al. describe "elements within both the NH_2-terminus and distal portions of the receptor are contributory to HIV-1 coreceptor activity, whereas neither element alone is essential," (page 1924, 3rd column, 1st paragraph). Thus, like Samson et al., Atchison fails to demonstrate that the elements missing in Li et al. are **necessarily inherent** in Li et al.

Applicants point out that Li et al. does not teach each and every aspect of the invention, and that the missing aspects from Li et al. are not inherently present, as the method of Li et al. would **not necessarily** lead to antibodies specific to the second extracellular loop of CCR5 and which inhibit binding of the noted chemokines MIP-1α, MIP-1β and RANTES. As discussed above, inherency "may not be established by probablilites or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." Continental Can Co. USA v. Monsanto Co. 948 F.2d 1264, 1269 (Fed Cir. 1991). In addition, the references cited teach or suggest that, contrary to the Examiner's assertion, the missing aspects from Li et al. are not necessarily inherent in Li et al., according to 35 USC §102, MPEP §706.02(IV), Atlas Powder Co. v. IRECO Inc, and Continental Can Co. USA v. Monsanto Co, as described above.

Hoxie

Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, and 207-208 were also rejected under 35 USC §102 (e) by the Examiner as being anticipated by Hoxie (U.S. Patent No. 5,994,515) as evidenced by Olson et al. (J Virol, May 1999; 73:4145-51), and Wu et al. (J Exp Med, October 1997; 186(8):1373-81).

Hoxie (U. S. Patent 5,994,515) describes a method to identify antibodies with anti-immunodeficiency activity. Hoxie used a hybridoma screening protocol in which mice were immunized with an SIV-infected human cell line in order to generate mAbs reactive with SIV envelope glycoproteins. Hoxie discloses eight mAbs which exhibited potent antiviral properties. According to Hoxie, "Of these eight MAbs, **seven reacted specifically with the viral envelope glycoproteins**, while **one antibody, MAb 12G5, reacted with both infected and uninfected cells**," (please see Hoxie, column 7, fourth full paragraph, emphasis added) and further stated, "the preferred antibody of the invention, **12G5, was discovered to bind to a cell protein termed CXCR4**, which protein is essential for entry of an immunodeficiency virus into cells," (Hoxie, column 7, fifth full paragraph, emphasis added) and "generation of an antiviral MAb specific for a cellular protein was unexpected." (Hoxie, Column 7, fourth full paragraph, emphasis added). None of the antibodies generated by Hoxie's screen bound any part of CCR5, and Hoxie does not disclose any example of an anti-CCR5 antibody. Hoxie does not disclose any mention of relevance of the second extracellular loop of CCR5 for any reason.

The Examiner appears to purport that the screen of Hoxie **necessarily** yields antibodies of the instant invention, namely those that specifically bind CCR5, block chemokine binding, and bind at the second extracellular loop of CCR5. The Examiner cites Olson et al. and Wu et al. as supporting references, and appears to argue that since at least one of the antibodies identified as "**most effective**" in blocking HIV infection binds the second extracellular loop of CCR5, that these antibodies are **necessarily inherent** in Hoxie. In effect, the Examiner appears to equate superior relative efficacy with inherency.

Applicants respectfully disagree. Hoxie discloses eight antibodies which exhibited potent inhibition of HIV infection. Of these, seven (87.5%) bound viral proteins. None (0%) of the antibodies bound CCR5 at any portion of CCR5. Hoxie does not disclose any example of an anti-CCR5 antibody, nor does Hoxie disclose any mention of relevance of the second extracellular loop of CCR5. Applicants submit that one of ordinary skill in the art would expect to find **100%** of the antibodies binding the second extracellular loop of CCR5 if such were **necessarily inherent** in Hoxie. The only antibody disclosed in Hoxie that blocks HIV and doesn't bind a viral protein, binds CXCR4, not CCR5.

Assuming even arguendo that antibodies which bind CCR5 at all would necessarily be identified using the screen of Hoxie, Olson et al. and Wu et al. both disclose antibodies that (1) block HIV infection, (2) bind CCR5, *but* (3) **do not** bind the second extracellular loop of CCR5 (they bind the N-terminus in both cases).

Olson et al., using a screening procedure that selected for HIV-1 inhibitory activity, isolated a panel of six mAbs with HIV-1 inhibitory activity. All six antibodies specifically bound CCR5. Through epitope mapping studies, Olson et al. identified the residues important for binding. Three (50%) of the antibodies disclosed by Olson et al. (termed PA8, PA11, and PA12) bound CCR5 in the N terminal domain (**and not the second extracellular loop**), and all of these inhibited HIV, with PA11 and PA12 exhibiting >90% inhibition of fusion (see Olson page 4151, column 1; and page 4152, middle of column 1). Thus, Olson et al. discloses a number of examples of antibodies which block HIV but do not bind the second extracellular loop of CCR5.

Wu et al. used a panel of anti-CCR5 antibodies to inhibit either chemokine binding or HIV-1 gp120 binding and HIV-1 infection. Using chimeric CCR2b/CCR5 receptors, Wu et al. mapped the domains on CCR5 recognized by these mAbs and correlated inhibitory activity with domain specificity of the mAbs. Wu et al. discloses that "efficient inhibition of an M-tropic HIV-1-derived envelope glycoprotein gp120 binding to CCR5 could be achieved with mAbs recognizing **either** the **second extracellular loop or** the **NH_2-terminal region**." (see Wu et al., abstract, emphasis added). Applicants submit that the teachings of Wu et al. highlight the diversity of anti-CCR5 antibodies capable of inhibiting HIV infectivity. Wu et al. discloses the antibody termed 3A9, which reacted only with chimeras that contained the NH_2-terminal region of CCR5, and that this 3A9 antibody exhibited significant inhibition of ^{125}I-gp120 binding (please see page 1375, paragraph spanning both columns;

pages 1377-1378 and Figure 6A). In addition, Wu et al. discloses that the 3A9 antibody, "directed to the NH_2-terminus of CCR5, caused minimal inhibition of binding of the three chemokines..." (see page 1376, paragraph spanning both columns). Thus, Wu et al. discloses at least one example of an antibody which blocks HIV but does not bind the second extracellular loop of CCR5, and does not inhibit chemokine ligand binding.

Furthermore, the Examiner appears to confuse Hoxie and Olson et al. at page 25 of the last Office action, where she stated, "As noted above Hoxie directs to the second extracellular domain (loop) and to antibodies to this second extracellular domain (loop)." Applicants respectfully point out that it is Olson et al. (May 1999) which mentions the second loop, and not Hoxie.

To summarize, both Olson et al. and Wu et al. disclose antibodies which inhibit HIV, by binding to the amino terminus rather than by binding to the second extracellular loop. Thus, the disclosures of these references demonstrate that the HIV inhibition screen of Hoxie would not necessarily result in identification of an antibody which binds CCR5, and even an antibody so identified would not necessarily bind CCR5 at the second extracellular loop, and inhibit chemokine binding. Therefore, antibodies with the instantly claimed characteristics would not necessarily be identified by the screen of Hoxie.

Olson et al. fails to demonstrate that the elements missing in Hoxie are **necessarily inherent** in Hoxie. Wu et al. also fails to demonstrate that the claimed characteristics of the antibodies of the instant invention are inherently present in Hoxie.

Applicants point out that Hoxie does not teach each and every aspect of the invention, and that the missing aspects from Hoxie are not inherently present, as the method of Hoxie would **not necessarily** lead to antibodies specific to CCR5, let alone antibodies specific to the second extracellular loop of CCR5 and which inhibit binding of the noted chemokines MIP-1α, MIP-1β and RANTES. Because Hoxie's method would not **necessarily** result in generation of an antibody with the characteristics of the instant claims, such characteristics are not **necessarily inherent** in Hoxie. As discussed above, inherency "may not be established by probablilites or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." Continental Can Co. USA v. Monsanto Co. 948 F.2d 1264, 1269 (Fed Cir. 1991). In addition, the references cited teach or suggest that, contrary to the Examiner's assertion, the missing aspects from Hoxie are not necessarily inherent in Hoxie, according to 35 USC §102, MPEP §706.02(IV), Atlas Powder Co. v. IRECO Inc, and Continental Can Co. USA v. Monsanto Co, as described above.

Littman et al.

Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, and 207-208 were rejected under 35 USC §102 (b) and (e)

by the Examiner as being anticipated by Littman et al. (U.S. Patent No. 5,939,320), as evidenced by Olson et al., and Wu et al.

As a preliminary matter, Applicants note that the rejection is not properly applied under 35 USC §102 (b) which applies when "the invention was patented or described in a printed publication in this or a foreign country, more than one year prior to the date of the application for patent in the United States," (35 USC §102 (b)). Littman et al. issued on August 17, 1999, which is not more than one year prior to Applicants' effective filing date, and indeed is after Applicants' effective filing date. Applicants respectfully request reconsideration and withdrawal of the rejection of claims under 35 USC §102(b).

With respect to the §102(e) rejection, Applicants respectfully disagree. Contrary to the Examiner's assertion, Littman et al. does not teach each and every aspect of the claimed invention. The screen of Littman et al. is generically directed to antibodies that recognize an HIV-translocating protein. Littman et al. merely identifies CCR5 as a mediator of HIV translocation, but gives no working examples, and makes no mention of the relevance of the second extracellular loop of CCR5, or inhibition of the binding of chemokines to CCR5. Furthermore, the screen of Littman et al. would **not necessarily** lead to antibodies which bind CCR5, let alone to antibodies specific to the second extracellular loop of CCR5 and which inhibit binding of the noted chemokines MIP-1α, MIP-1β and RANTES.

The Examiner also appears to purport that the screen of Littman et al. **necessarily** yields the antibodies of the instant invention, namely those that specifically bind CCR5, block chemokine binding, and bind at the second extracellular loop of CCR5. The Examiner cites Olson et al. and Wu et al. as supporting references, and appears to argue that since at least one of the antibodies identified as "**most effective**" in blocking HIV infection binds the second extracellular loop of CCR5, that these antibodies are **necessarily inherent** in Littman et al. In effect, the Examiner appears to equate superior relative efficacy with inherency.

As discussed above, Olson et al. and Wu et al. both disclose antibodies that (1) block HIV infection, (2) bind CCR5, *but* (3) **do not** bind the second extracellular loop of CCR5 (they bind the N-terminus in both cases).

Applicants reiterate their arguments in view of Olson et al. and Wu et al. in response to the Examiner's §102 rejection based on Hoxie above.

To summarize, both Olson et al. and Wu et al. disclose antibodies which inhibit HIV, by binding to the amino terminus rather than by binding to the second extracellular loop. Thus, the disclosures of these references demonstrate that the HIV inhibition screen of Littman et al. would not necessarily result in identification of an antibody which binds CCR5, and even an antibody so identified would not necessarily bind CCR5 at the second extracellular loop, and inhibit chemokine binding. Therefore, antibodies with the instantly claimed characteristics would not necessarily be identified by the screen of Littman et al.

Applicants point out that Littman et al. does not teach each and every aspect of the invention, and that the missing aspects from Littman et al. are not inherently present, as the method of Littman et al. would **not necessarily** lead to antibodies that bind CCR5, let alone antibodies specific to the second extracellular loop of CCR5 and which inhibit binding of the noted chemokines MIP-1α, MIP-1β and RANTES. Because the method of Littman et al. would not **necessarily** result in generation of an antibody with the characteristics of the instant claims, such characteristics are not **necessarily inherent** in Littman et al. As discussed above, inherency "may not be established by probablilites or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." Continental Can Co. USA v. Monsanto Co. 948 F.2d 1264, 1269 (Fed Cir. 1991). In addition, the references cited teach or suggest that, contrary to the Examiner's assertion, the missing aspects from Littman et al. are not necessarily inherent in Littman et al., according to 35 USC §102, MPEP §706.02(IV), Atlas Powder Co. v. IRECO Inc, and Continental Can Co. USA v. Monsanto Co, as described above.

That the "most effective" HIV blocking, anti-CCR5 antibodies were later found by Olson et al. or Wu et al. to bind the second extracellular loop of CCR5, does not make these characteristics necessarily inherent in Hoxie or Littman et al. That Olson et al. and Wu et al. also found HIV blocking antibodies which did not bind CCR5, or bound CCR5 at places other than the second extracellular loop, demonstrates that the screens of Hoxie and Littman et al. do not necessarily include the claimed limitations of the antibodies of the instant invention.

Because Li et al. does not teach every aspect of the claimed invention either explicitly or impliedly, Li et al. does not anticipate the invention of the instant claims.

Because Hoxie et al. does not teach every aspect of the claimed invention either explicitly or impliedly, Hoxie et al. does not anticipate the invention of the instant claims.

Because Littman et al. does not teach every aspect of the claimed invention either explicitly or impliedly, Littman et al. does not anticipate the invention of the instant claims.

Therefore, Applicants respectfully request reconsideration and withdrawal of the rejections of claims under 35 USC §102.

The Rejections of Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, and 207-208

Under 35 USC §103(a) Should Be Withdrawn

Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, and 207-208 were rejected under 35 USC §103(a) as being unpatentable over Chuntharapai et al. (U.S. Patent No. 5,543,503), in view of either Raport et al. (JBC, July 1996; 271:17161-17166), Samson et al. (Biochem., March 1996; 35:3362-3367), or Combadiere et al. (J Leukoc Biol, July 1996; 60:147-152), as evidenced by Wu et al (J Exp Med, October 1997; 186(8):1373-1381).

Specifically, the Examiner argued, "Chuntharapai notes the suggestion of making antibodies specific for a chemokine family receptor such that antibodies bind and inhibit receptor function." The Examiner stated that the suggestion and reasonable expectation of success are provided. The Examiner appears to take the position that selection of antibodies that are inhibitory to ligand binding is evidenced to be routine in the art as noted in Chuntharapai et al., and that the skill in the art is quite high.

Applicants respectfully disagree. Chuntharapai et al. makes no suggestion of CCR5 or antibodies that bind CCR5, and does not teach antibodies which inhibit functions associated with ligand binding. None of the references cited teach or suggest an antibody which binds to the second extracellular loop of CCR5, with the exception of Wu et al., which was published after the filing date of the instant application. Therefore, the cited references do not teach or suggest all the limitations of the antibodies of the instant invention.

Applicants further submit that Chuntharapai et al. (who teach preparation of antibodies capable of binding to human IL-8 receptors), alone or in combination with the cited references, does not provide a reasonable expectation of success for making antibodies of the instant invention. For example, Chuntharapai, in another published study (Chuntharapai et al., February 1994; J Immunol 152(4):1783-1789, see Supplemental Information Disclosure Statement filed herewith) teaches that blocking monoclonal antibodies to human IL-8 Receptor A bind to the N-terminus of the IL-8A Receptor. Chuntharapai et al. (J Immunol) points out that, among IL-8 Receptor types A and B, the N-terminal region of the receptor has the least sequence homology between IL-8A and IL-8B, despite 77% amino acid sequence identity between the two receptor types. Further, Chuntharapai et al (J Immunol) states,

> "when trying to generate mAbs to other chemokine receptors, it may be a valuable strategy to 1) concentrate on peptide immunogens corresponding to NH_2-terminal sequences **rather** than other regions of the receptor..." (emphasis added).

Furthermore, Ahuja et al. (JBC, January 1996; 271(1):225-232), see Supplemental IDS filed herewith) teaches that, even within the subtype of IL-8 receptors, ligand selectivity differs, and that ligand binding and activation are separable. Thus, the teachings of Chuntharapai et al., relating to antibodies to the IL-8 Receptor, do not provide an expectation of success in making the claimed antibodies of the instant

invention, since, for example, they specifically guide away from the second extracellular loop of a chemokine receptor.

Contrary to the Examiner's assertion, as described above, the art actually teaches away from requirement for binding the second extracellular loop of the chemokine receptor CCR5 for making antibodies of the instant invention. Thus, the art gives no expectation of success for making the antibodies with all the limitations of the instantly claimed invention, namely an "antibody or antigen binding fragment thereof which binds to the second extracellular loop of a human chemokine receptor 5 (CCR5), wherein said antibody or antigen binding fragment inhibits binding of a chemokine to the receptor, wherein said chemokine is MIP-1α, MIP-1β, RANTES, or a combination thereof, and wherein said antibody or antigen binding fragment thereof inhibits one or more functions associated with binding of the chemokine to the receptor." Such antibodies as those claimed in the instant application would not be obvious under 35 USC §103(a). Therefore, Applicants request reconsideration and withdrawal of the rejections of claims 147, 168, 189, and claims dependent therefrom, under 35 USC §103(a).

With respect to claims directed to antibodies which also block HIV infection (claims 158, 179, 200, and claims dependent therefrom), one of skill in the art would further not have an expectation of success to develop the antibodies with all the limitations of the instantly claimed invention, wherein those antibodies block HIV infection, since the only reference cited which mentions HIV is Combadiere et al., which only suggests CCR5 as a mediator of HIV replication by virtue of the ability of MIP-1α, MIP-1β, RANTES to affect HIV replication, but do not give any examples of antibodies which bind CCR5, let alone the second extracellular loop of CCR5 and inhibit chemokine ligand binding. Thus, such antibodies, further including the limitation wherein they block HIV infection, would not be obvious under 35 USC §103(a). Therefore, Applicants request reconsideration and withdrawal of the rejections of claims 158, 179, 200, and claims dependent therefrom, under 35 USC §103(a).

Applicants submit that Chuntharapai et al. with Raport et al., Samson et al., or Combadiere et al., and Wu et al., does not teach or suggest all of the limitations of the instant claims, either alone or in combination. Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection of claims under 35 USC §103(a).

In addition, Claims 147-148, 150-153, 155-156, 158-163, 165-166, 168-169, 171-174, 176-177, 179-184, 186-187, 189-190, 192-195, 197-198, 200-205, and 207-208 were rejected under 35 USC §103(a) as being unpatentable over Chuntharapai et al., in view of either Raport et al., Samson et al., or Combadiere et al., as evidenced by Wu et al., *further in view of Ramakrishnan et al.* (U.S. Patent No. 5,817,310).

Applicants respectfully disagree. As discussed above, Chuntharapai et al. with Raport et al., Samson et al., or Combadiere et al., and Wu et al., does not teach or suggest all of the limitations of the instant claims, either alone or in combination. The teachings of Ramakrishnan et al. describe antibodies

and fragments thereof that bind a human growth factor receptor, PDGF beta, including chimeric antibodies, yet fail to remedy the deficiencies of the cited references. Thus, Ramakrishnan et al., either alone or in combination with the other cited references, does not render the presently claimed invention obvious. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSIONS

In view of the remarks and amendments made herein, Applicants respectfully submit that the objections and rejections presented by the Examiner are now overcome and that this application is in condition for allowance. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

This paper is being filed timely as a request for two month extension is filed concurrently herewith. Applicants believe no further extensions of time are required. In the event any additional extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Entry of the remarks made herein is respectfully requested.

Respectfully submitted,

November 22, 2005

MILLENNIUM PHARMACEUTICALS, INC.

By _____

Jean M. Silveri
Registration No. 39, 030
40 Landsdowne Street
Cambridge, MA 02139
Telephone - 617-679-7336
Facsimile - 617-551-8820

APPENDIX A

	Present Application No. 09/870,932, filed May 30, 2001	**Parent Application No. 08/893,911, filed July 11, 1997 (now U.S. Patent 6,528,625)**	**Grandparent Application No. 08/739,507, filed October 28, 1996 (now abandoned)**
Claim Term	*Support at:*	*Support at:*	*Support at:*
human CCR5	page 3, lines 21-22, 25-26 page 11, lines 18-20 Claim 2 as originally filed	page 4, lines 10-12, 16-21 page 13, lines 31-33 Claim 2 as originally filed	page 3, lines 16-18 page 7, lines 22-24 Claim 2 as originally filed
chemokines (MIP-1α, MIP-1β and RANTES) or combination thereof	page 1, line 14 through page 2, line 5 page 3, lines 2-5 page 12, lines 1-3 Claims 30, 31 and 33 as originally filed	page 1, line 9 through page 2, line 14 page 14, lines 14-17 page 3, lines 17-18 page 7, lines 20-22 Claims 30, 31 and 33 as originally filed	page 1, lines 11-28 page 2, line 26 page 8, lines 6-9
inhibits one or more functions associated with binding of a chemokine to the receptor	page 3, lines 21-28 page 11, line 21 through page12, line 3 Claim 45 as originally filed	page 4, line 10-21 page 14, lines 2-24 Claim 45 as originally filed	page 3, lines 16-22 page 8, lines 3-9 Claim 5 as originally filed
human antibodies	page 14, lines 25-28	page 17, lines 29-34	
chimeric antibodies	page 15, lines 3, 4, 17	page 18, lines 5-9	page 10, lines 15-19
humanized antibodies	page 15, lines 3-6 and 18 page 16, lines 10-17	page 18, lines 5-9 page 19, lines 24-34	page 10, lines 15-19
binds the second extracellular loop	page 12, line 28 through page 13, line 1 Claim 27 as originally filed	page 15, lines 18-21 Claim 27 as originally filed	
inhibits HIV infection	page 7, line 17 through page 8, line 3 page 37, line 26 through page 38, line 1 page 59, line 24 through page 60, line 23 Claims 12, 15 and 25 as originally filed	page 9, lines 6-31 page 48, lines 1-28 Claims 12, 15 and 25 as originally filed	page 5, lines 3-28 page 27, line 31 through page 28, line 23 Claims 6, 11, 15 and 25 as originally filed